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2. GOVT ACCESSION NO. | 3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle)

Beneficial effect of dexamethasone in decreasing the lethality of acute T-2 toxicosis

5. TYPE OF REPORT & PERIOD COVERED

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)

Robert F. Fricke

8. CONTRACT OR GRANT NUMBER(s)

9. PERFORMING ORGANIZATION NAME AND ADDRESS

US Army Medical Research Institute of Infectious Diseases, SGRD-UIS-D
Fort Detrick, Frederick, MD 21701-5011

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS

11. CONTROLLING OFFICE NAME AND ADDRESS

US Army Medical Research and Development Command

12. REPORT DATE

7 November 1986

13. NUMBER OF PAGES

21

14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)

15. SECURITY CLASS. (of this report)

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Distribution unlimited - Approved for public release

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

To be published in Toxicology and Applied Pharmacology

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

T-2 toxin, trichothecene mycotoxins, dexamethasone, anti-inflammatory glucocorticoid

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Steroidal and non-steroidal anti-inflammatory agents were evaluated for effectiveness for treatment of acute T-2 toxicosis in mice. Non-steroidal agents, indomethacin, phenylbutazone, and acetylsalicylic acid, were either ineffective, or potentiated the lethality of T-2 toxin. Steroidal agents, assessed at equivalent doses for anti-inflammatory activity, were all effective, with dexamethasone being more effective than either methylprednisolone or hydrocortisone. The doses of dexamethasone producing the highest efficacy were 1.0 mg/kg and 12.5 mg/kg for im and ip routes of administration, respectively.

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Beneficial effect of dexamethasone in decreasing the lethality of acute T-2 toxicosis

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RUNNING TITLE: Dexamethasone treatment of T-2 toxicosis

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Beneficial effects of dexamethasone in improving survival in acute T-2 toxicosis. Fricke, R. F. (1986). Toxicol. Appl. Pharmacol. , - .

Steroidal and non-steroidal anti-inflammatory agents were evaluated for effectiveness for treatment of acute T-2 toxicosis in mice. Non-steroidal agents, indomethacin, phenylbutazone, and acetylsalicylic acid, were either ineffective, or potentiated the lethality of T-2 toxin. Steroidal agents, assessed at equivalent doses for anti-inflammatory activity, were all effective, with dexamethasone being more effective than either methylprednisolone or hydrocortisone. The doses of dexamethasone producing the highest efficacy were 1.0 mg/kg and 12.5 mg/kg for im and ip routes of administration, respectively. The mean time to death, mean survival time, and percent lethality were determined for untreated and dexamethasone-treated mice injected with a lethal dose of T-2 toxin. Dexamethasone (13 mg/kg, ip) was administered 1 hr before, the same time as, or 1, 2, and 3 hr after injection of T-2 toxin (5 mg/kg, sc). Compared to 100% lethality for untreated mice, dexamethasone at all of the treatment times significantly decreased lethality. As the time between toxin exposure and treatment was increased, there was a corresponding increase in lethality. The mean times to death and mean survival times were also determined and, in all cases, were found to be greater in the treated groups. In conclusion, steroidal, but not non-steroidal, anti-inflammatory agents were effective in decreasing T-2 toxin-induced lethality. All of the anti-inflammatory glucocorticoids were effective with dexamethasone producing the highest efficacy. Dexamethasone was most effective when administered before exposure to toxin, with decreasing efficacy as treatment was delayed.

T-2 toxin, a trichothecene mycotoxin produced by Fusarium fungi, has been implicated as the causative agent in disease states in both humans and animals. The development of certain diseases in humans, such as alimentary toxic aleukia (Saeburg and Strong, 1971), and in livestock, such as moldy corn toxicosis (Hsu et al., 1972), are directly attributed to the consumption of toxin-contaminated food or grain. Potential therapy for treatment of mycotoxin-induced diseases was recently reviewed by the National Academy of Science (NAS). The NAS report (1983) concluded that no specific treatment, other than supportive or symptomatic, was available for trichothecene mycotoxicoses.

The characteristic symptoms of T-2 toxicosis include the development of vomiting, diarrhea, leukopenia, and anemia (Ueno, 1984). Further, experimentally-induced acute T-2 toxicosis in rats, guinea pigs, swine, and other experimental animals (Feuerstein et al., 1985; Lorenzana et al., 1965; Sato et al., 1975) results in the development of a shock-like state, with the characteristic alterations in heart rate, cardiac output, and mean arterial blood pressure.

Various forms of shock are effectively managed by the intensive, short-term use of anti-inflammatory glucocorticoids at relatively high doses (Adams and Parker, 1979; Lefer and Spath, 1977; MacDonald, 1982; Rosenthal and Wilke, 1983). Since T-2 intoxication results in shock-like syndrome, glucocorticoids were evaluated for prophylaxis and therapy of lethal T-2 intoxications. In preliminary studies Tremel et al. (1985) found that the glucocorticoid dexamethasone was an effective treatment for acute T-2 toxicosis in rats. In this study, the efficacy of both steroidal and non-steroidal anti-inflammatory agents for the treatment of acute T-2 toxicosis was evaluated in mice.

METHODS

Animals. Male mice (Swiss ICR), with a mean body weight (± SD) of 24.3 ± 2.61 g, were obtained from Buckberg Lab Animals (Tompkins Cove, N. Y.). Mice were maintained in animal rooms with controlled temperature (21-22 °C.), humidity (45-50%), and regular light cycles (12 hr). Animals were housed in wire-bottom cages and allowed feed and water ad libitum. After a 1 week acclimation period, the animals were prescreened by body weight and randomly assigned to control and treatment groups.

Toxin and drugs. T-2 toxin (Myco-Labs, Chesterfield, Mo.), 99% purity, was dissolved in 100% ethanol to yield a stock solution of 25 mg/ml. Before use the stock toxin solution was diluted with propylene glycol:ethanol (90:10) to the desired concentration. LD50 values for T-2 toxin were determined using six equally spaced logarithmical doses of 1 to 5 mg/kg. Groups of 10 mice/dose were injected sc with 100 µl of toxin.

Dexamethasone sodium phosphate (Hexadrol®, Organon, Inc., W. Orange, N.J.), methylprednisolone sodium succinate (A-Methapred®, Abbott Laboratories, N. Chicago, Ill.), and hydrocortisone sodium succinate (Solu-Cortef®, The Upjohn Comp., Kalamazoo, Mich.) were diluted with sterile saline before use. The non-steroidal anti-inflammatory agents, indomethacin, phenylbutazone, and acetylsalicylic acid (all obtained from Sigma Chemical Co., St. Louis, Mo.) were diluted with sterile saline before use. Injection volumes were 100 µl and 50 µl for ip and im administration, respectively. Untreated animals received an equal volume of sterile saline.

Data Analyses. Determination of LD50 values and associated calculations were determined by probit regression analysis (Finney, 1971). Slopes of the probit regression were calculated and, if found to be not significantly different from each other by X^2 analysis, the data were recalculated using the best fit common slope. Relative potency values (LD50(treated)/LD50(untreated) were calculated from the common slope LD50 values for T-2 toxin. Comparisons for statistical significance between untreated and treated groups were carried out by least significant difference analysis on the pooled variance of the LD50 values (Steel and Torrie, 1960).

The time courses for the cumulative percent survival of treated and untreated mice were used to determine the mean survival times and the mean time to death values. Mean survival times were determined by survival analysis using the Kaplan-Meier product limit of the cumulative survival curve, with statistical significance determined by the Mantel-Cox and Breslow-Wilcoxon hypothesis tests (BMDP Statistical Software, Los Angeles, Calif.). The mean survival times were determined from both censored (dead animals) and uncensored (alive animals) data for each treatment group with a terminal observation time limit of 72 hr. The times to death of the animals were analysed by univariant analysis with pair-wise comparisons for statistical significance (SAS Institute Inc., Cary, N.C.). The percent lethalities were calculated after 72 hr and significant differences between treated and untreated groups were determined by the Fisher's exact test (Gad and Weil, 1982).

RESULTS

Effectiveness of steroidal and non-steroidal anti-inflammatory agents. The efficacy of steroidal and non-steroidal anti-inflammatory agents for treatment of acute T-2 toxicosis was assessed in mice. Compared to the control LD50 value for T-2 toxin, treatment with indomethacin or phenylbutazone potentiated lethality, while acetylsalicylic acid was ineffective (Table 1). However, mice treated with glucocorticosteroids at equivalent doses for anti-inflammatory activity (Sayers and Travis, 1970) all showed improved survival (Table 1). Since dexamethasone showed the highest efficacy, further experiments were carried out with this drug.

Effect of dexamethasone dose and route of administration on lethality of T- 2 toxin. The effect of dexamethasone dose and route of administration on the lethality of T-2 toxin was determined (Table 2). Mice were injected sc with T-2 toxin and were immediately administered either saline or dexamethasone sodium phosphate at the indicated doses and routes of administration. LD50 and relative potency values were determined 48 hr after toxin injection. Dexamethasone treatment, by either route of administration, resulted in significant increases in the LD50 and relative potency values. The highest efficacy was achieved at an ip dose of 12.5 mg/kg, while im administration produced equal protection at 1 mg/kg.

Effect of time of dexamethasone administration on lethality of T-2 toxin. The efficacy of dexamethasone administered either before, the same time as, or after injection of a lethal dose of T-2 toxin was determined. The cumulative percent survival of mice in the different treatment groups was determined at approximately 2 hr intervals for a total observation time of 72 hr (Fig. 1). The untreated mice showed an accelerated decline in the percent survival,

reaching 0% 23 hr after toxin administration. All of the dexamethasone-treated mice groups showed improved survival, with 1 hr pretreatment producing higher survival than either simultaneous or postexposure treatment.

The survival curves were analyzed to determine the effect of treatment time on the time to death, survival time, and percent lethality (Table 3). Mice were treated with dexamethasone either before, the same time as, or at different times after a lethal dose of T-2 toxin. Pretreatment with dexamethasone was more effective than treatment at the same time as or after injection of T-2 toxin. Animals pretreated with dexamethasone showed the lowest percent lethality. As treatment was delayed, there was a progressive decrease in the percent lethality, reaching 80% when treatment was delayed 2-3 hr. All of the survival times for dexamethasone-treated mice were significantly higher than untreated controls. Pretreatment with dexamethasone resulted in the longest survival time, but the time was not significantly different from the other treatment times. The survival times for simultaneous or delayed treatment were all approximately the same, with no apparent correlation between treatment time and the survival time. The times to death for the dexamethasone-treated groups were all higher than untreated controls. There was no correlation between either the time to death or the degree of significance for the different treatment times. For all of the treated groups, mean time to death values averaged 29.8 hr, a twofold increase over the value of 14.4 for untreated controls.

DISCUSSION

Although all of the glucocorticoids tested afforded significant protection against the lethal effects of T-2 toxin, dexamethasone showed the greatest efficacy when compared to equivalent anti-inflammatory doses of either prednisolone and hydrocortisone. The low efficacy of prednisolone and hydrocortisone suggests that either the protective effect may not be directly related

to their anti-inflammatory activity, or that the doses of these steroids were not optimum. Vargish et al. (1976) showed that dexamethasone at 15 mg/kg or methylprednisolone at 30 mg/kg produced the highest efficacy in partially reversing hypotension in hemorrhagic shock. If doses higher than these were used, the anti-hypotensive effect was decreased. Further, methylprednisolone at 60 mg/kg, a dose approximately equivalent in anti-inflammatory activity to the optimal dexamethasone dose (15 mg/kg), was not only less effective, but also increased the degree of hypotension.

The most effective dose of dexamethasone for treatment of T-2 toxicosis was determined for both ip and im routes of administration. There was a clear dose-response relationship between the dose of steroid administered and the resulting relative potency value. The most effective doses of dexamethasone were 12.5 mg/kg and 1.0 mg/kg for ip and im administration, respectively. This marked difference in the effective doses by these two routes of administration may be due to differences in release, rates of absorption, or metabolism.

The protective effect of dexamethasone in the mouse substantiates a previous report for the treatment of T-2 toxicosis in the rat (Tremel et al., 1985). In this report, dexamethasone treatment (1.6 mg/kg, iv) either 30 min before or 1 hr after T-2 toxin administration (0.75 mg/kg, iv) resulted in significant reduction in the percent lethality. At a higher dose of toxin (1 mg/kg, iv), rats pretreated with dexamethasone had survival times of 19 hr compared to 9 hr for untreated animals. Although dexamethasone prolonged the onset of death, the overall mortality rate was not altered.

There is not, however, full agreement on the efficacy of steroids in treatment of T-2 toxicosis. In contrast to the data presented here and by Tremel et al. (1985), Ueno et al. (1984) found that pretreatment with prednisolone was not an effective therapy. The ineffectiveness of prednisolone might be due to

the length of time (24 hr) between the final steroid dosing and toxin challenge. Imai et al. (1979) showed that glucocorticoid pretreatment times greater than 3 hr were ineffective in decreasing the lethality of endotoxin-treated mice. Further, pharmacokinetic studies in dogs showed that the mean plasma half-life of prednisolone was 166 min (Hankes et al., 1985). This finding suggests that the plasma prednisolone concentration in mice might have reached ineffective levels after 24 hr.

The timing for the administration of glucocorticoids may be critical for decreasing the lethality of T-2 toxin, since there are clear indications that delayed treatment results in reduced efficacy. A single bolus injection of dexamethasone (13 mg/kg, ip), given 1 hr before administration of T-2 toxin, was more effective than either simultaneous or delayed treatment. As the time interval between toxin injection and steroid treatment was increased there was a marked decrease in efficacy as measured by the percent lethality. These findings are similar to those reported for the treatment of endotoxin shock in baboons. When the time between endotoxin infusion and treatment with methylprednisolone was increased, the survival rate was markedly decreased (Archer et al., 1983). Similarly, for treatment of septic shock in rats, Ottosson et al. (1982) demonstrated a direct correlation between the onset of glucocorticoid therapy and the resulting survival times.

Schaefer et al. (1983) showed that large doses of methylprednisolone were effective when administered after the onset of hypotension during endotoxin shock. The treated animals showed not only improvement in cardiovascular and metabolic parameters, but also significantly higher survival after 24 hr. Although a similar treatment schedule has not been evaluated for T-2 toxicosis, available data indicate a rapid onset of the effect of toxin on cardiovascular function. Within 10 min after an iv bolus injection of T-2 toxin into conscious rats, there was a decrease in hindquarter blood flow, which was

mirrored by an increase in vascular resistance (Siren and Feuerstein, 1986). These findings suggest a rapid development of the toxicosis, which would indicate that steroid treatment should be initiated as early as possible.

In summary, the present study indicates that glucocorticosteroids were beneficial in protecting mice against the lethal effects of T-2 toxin. The mechanism for the protective effect of steroids in the treatment of T-2 toxicosis is, at present, not known. However, as summarized by Haakes (1976), the beneficial action of glucocorticoids may be due, in part, to (1) improved cardiac function and improved vascular perfusion, (2) increased metabolism of lactic acid, (3) stabilization of lysosomal membranes, and (4) improved energy production. For these proposed actions of glucocorticoids, there is a corresponding observation concerning T-2 toxicosis. Thus, glucocorticoids may be an effective treatment for T-2 toxicosis by attenuation of (1) the development of shock, as previously discussed; (2) lactic acidosis (Feuerstein et al., 1985); (3) lysosomal enzyme release (Fricke, 1985); and (4) decreased energy metabolism (Pace, 1983).

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FOOTNOTES

1. Presented in part at the 24th Annual Meeting of the Society of Toxicology in March, 1985, San Diego, Ca. and the 8th World Congress on Animal, Plant, and Microbial Toxins in August, 1985, Newcastle upon Tyne, U.K..

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", as promulgated by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

Table 1.

EFFECT OF STEROIDAL AND NON-STEROIDAL ANTI-INFLAMMATORY AGENTS ON LD50 VALUES FOR T-2 TOXIN[a]

DRUG	DOSE (mg/kg, ip)	LD50[b] (mg/kg, sc)
Nonsteroidal agents		
Saline	—	3.22 (2.54-4.14)
Indomethacin	10	1.78 (1.41-2.23)***[c]
Phenylbutazone	100	2.14 (1.65-2.74)***
Acetylsalicylic acid	300	2.69 (2.10-3.54)
Steroidal agents		
Saline	—	2.40 (1.55-3.47)
Dexamethasone	10	3.91 (2.45-10.6)**
Methylprednisolone	53	3.47 (2.06-9.40)*
Hydrocortisone	266	3.00 (1.83-6.70)

[a] Mice were injected sc with T-2 toxin and treated immediately with the drugs listed at the indicated doses.

[b] LD50 values for T-2 toxin were determined 48 hr after administration of toxin. Values in parenthesis represent 95% confidence intervals for the LD50 value.

[c] Significant difference compared to corresponding control value, $p<0.05$, *; $p<0.01$, **; $p<0.001$, ***.

Table 2

EFFECT OF ROUTE OF ADMINISTRATION AND DOSE OF DEXAMETHASONE ON LD50 AND RELATIVE POTENCY VALUES OF T-2 TOXIN[a]

ROUTE OF ADMINISTRATION	DOSE (mg/kg)	LD50[b] (mg/kg)	RELATIVE POTENCY[c]
ip	0.0	2.46 (1.97-3.19)	1.00
	0.125	2.77 (2.14-4.33)	1.13
	1.25	3.09 (2.40-4.97)*[d]	1.26
	12.5	4.04 (3.10-6.99)***	1.64
im	0.0	2.28 (1.83-2.80)	1.00
	0.1	2.43 (1.25-3.41)	1.06
	0.25	3.54 (2.93-4.38)***	1.55
	1.0	3.75 (2.93-5.08)***	1.64

[a] Mice were injected sc with T-2 toxin and immediately administered with either saline vehicle (0 mg/kg) or dexamethasone sodium phosphate at the indicated doses and routes of administration. Volumes for ip and im injections were 100 µl and 50 µl, respectively.

[b] The LD50 values were determined 48 hr after the administration of T-2 toxin. The values in parenthesis represent the 95% confidence intervals for the LD50 values.

[c] Relative potency = LD50 (dexamethasone-treated)/LD50 (saline-treated)

[d] Significant difference compared to corresponding control value, $p<0.05$, * and $p<0.001$, ***.

Table 3

EFFECT OF DEXAMETHASONE TREATMENT TIME ON TIME TO DEATH, SURVIVAL TIME, AND PERCENT LETHALITY OF T-2 TOXIN IN MICE[a]

TIME (hr)	TIME TO DEATH[b] (hr)	SURVIVAL TIME (hr)[c]	% LETHALITY[d]
CONTROL	14.4 ± 0.81 (n=20)	14.4 ± 0.81	100
-1	32.5 ± 5.18***[e] (n=8)	56.2 ± 5.07*	40***
0	25.3 ± 4.28 (n=12)	44.0 ± 5.92***	60**
+1	33.4 ± 5.73 (n=14)	45.0 ± 5.50***	70**
+2	35.1 ± 5.40*** (n=15)	42.5 ± 5.50***	80*
+3	22.5 ± 3.24 (n=16)	42.3 ± 5.99***	80*

[a] Mice (20/group) were treated with dexamethasone (13 mg/kg, ip) before (-), the same time as, or at different times after (+) injection with T-2 toxin (5 mg/kg, sc). Control mice were injected at the same time with saline (100 µl) and T-2 toxin.

[b] Mean ± SE. Number of observations (n) is indicated in parentheses.

[c] Mean survival times (± S.E., n = 20/group) were calculated with a limiting time of 72 hr.

[d] The percent lethality was determined at the end of the 72 hr observation period.

[e] Significant difference compared to corresponding control value, $p<0.05$, * $p<0.01$, **; $p<0.001$, ***.

LIST OF FIGURES

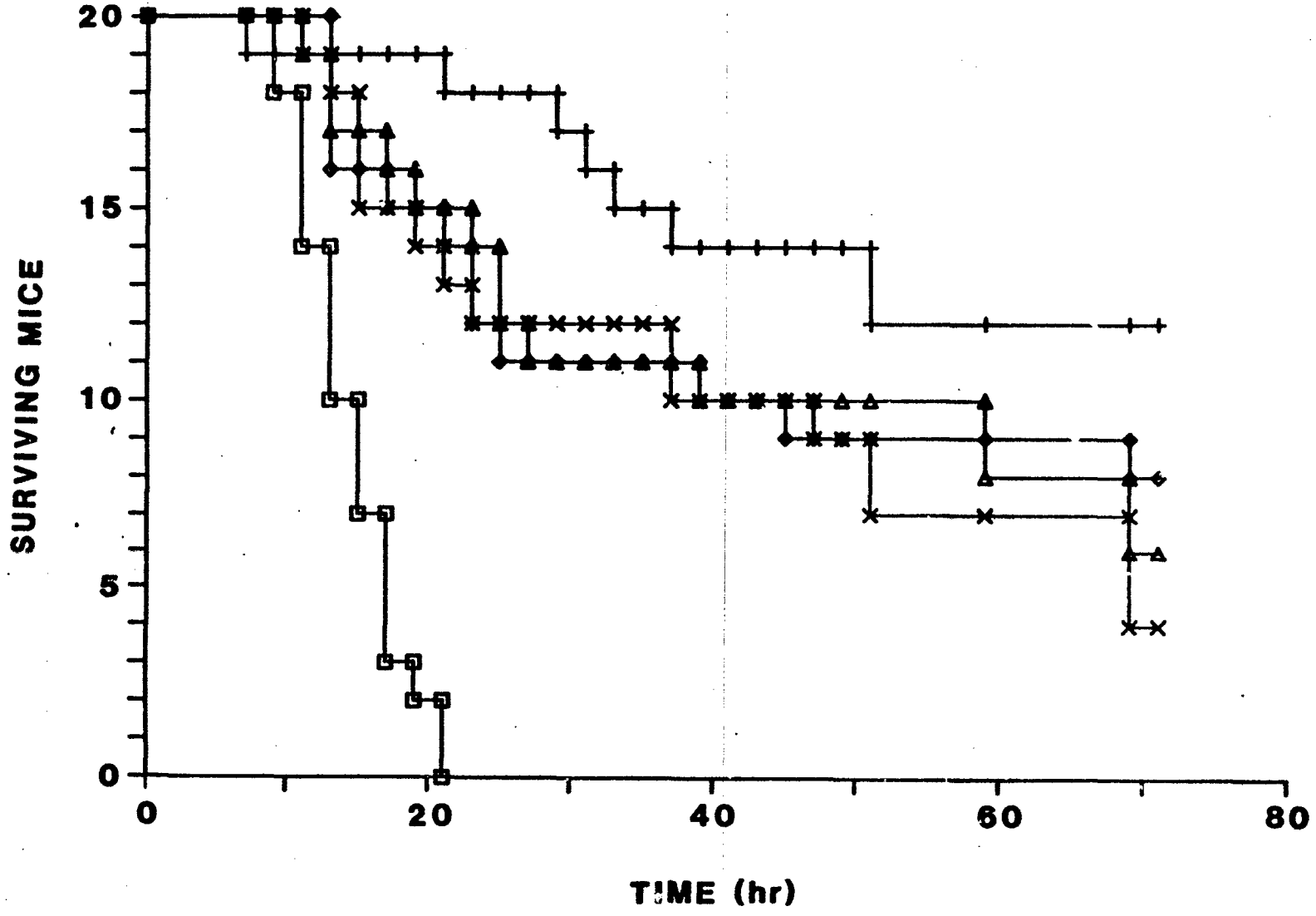
INDEX TERMS

T-2 toxin

Trichothecene mycotoxins

Dexamethasone

Anti-inflammatory glucocorticoids


SURVIVING MICE
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